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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,313	09/28/2005	Michiaki Nagasawa	2005-0859A	8378

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EXAMINER	
RAHMANI, NILOOFAR	
ART UNIT	**PAPER NUMBER**
1625	

MAIL DATE	DELIVERY MODE
07/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,313	NAGASAWA ET AL.	
	Examiner	Art Unit	
	Niloofar Rahmani	1625	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 are currently pending in the instant application.

Priority

2. This application is filed on 09/28/2005, which is a 371 of PCT/JP03/15315, filed on 12/01/2003, which claims the priority of JAPAN 2002-350804, filed on 12/03/2002.

3. *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-10 are rejected because the term "therapeutic" is confusing. Does it mean "pharmaceutical composition" or "method for treating a disease"? Correction is required.

4. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims.
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to a therapeutic or prophylactic agent for Parkinson's disease, Huntington's disease, Alzheimer's disease, Schizophrenia.

The state of the prior art: " In inflammatory cells, intracellular cAMP concentration is regulated by cyclic nucleotide phosphodiesterases 4. therefore,

PDE4 inhibition appears as a rational goal for treating acute or chronic inflammatory diseases. knowing the contribution of PDE4 in PBMCs to the LPS response (54), considering the high TNF-α levels associated with a number of inflammatory and autoimmune disorders- for revue see (40)- and the success of TNF-α antibodies and soluble receptors in the treatment of these diseases, provides support for the hypothesis that they may be efficiently treated with specific PDE4 inhibitors." (Reimund et al., Biochemical and biophysical research communications, 2001, Vol. 288, pages 427-434).

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject.

Amount of guidance/working examples: On pages 8-11 of the specification, applicant has examples of test compounds for inhibition of PDEs by Ibudilast. However, applicant has not guidance or examples for treating Parkinson's disease, Huntington's disease, Alzheimer's disease, Schizophrenia using the compounds in claim 1.

The breadth of the claims: The breadth of claims is drawn to a therapeutic or prophylactic agent for Parkinson's disease, Huntington's disease, Alzheimer's disease, Schizophrenia.

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating Parkinson's disease, Huntington's disease, Alzheimer's disease, Schizophrenia, one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claims 3-10, for treating a therapeutic or prophylactic agent for Parkinson's disease, Huntington's disease, Alzheimer's disease, Schizophrenia, using a compound of formula I according to claim 1, have been enabled by the instant specification.

5. Claims 3-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being possibly enabling for treating specific diseases, does not reasonably provide enablement for preventing diseases. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 11,page 4 to line 14, page 4lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to medical treatment and are therefore physiological in

nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become afflicted before the fact. 6) The artisan using Applicants invention would be a Board Certified physician who specialized to treat diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of Parkinson's, Huntington's, Alzheimer's diseases, schizophrenia generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent Parkinson's, Huntington's, Alzheimer's diseases, schizophrenia generally. That is, the skill is so low that no compound effective generally against Parkinson's, Huntington's, Alzheimer's diseases, schizophrenia has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not

just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formula (1).

The Examiner suggests deletion of the word "prevention".

6. *Claim Rejections - 35 USC § 102*

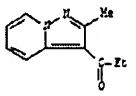
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

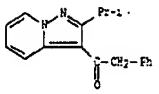
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kouno et al. US 6,265,577. Kouno et al. disclosed the instant claimed compounds, which form the STN search are

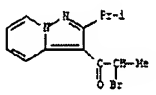
RN 151831-27-5
CN 1-Propanone, 1-(2-methylpyrazolo[1,5-a]pyridin-3-yl)-



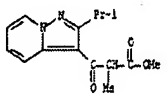
RN 204504-62-1
CN Ethanone, 1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-phenyl-



RN 204504-63-2
CN 1-Propanone, 2-bromo-1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-



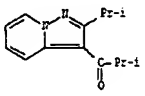
RN 141418-12-4
CN Pyrazolo[1,5-a]pyridine-3-propanoic acid, a-methyl-2-(1-methylethyl)-b-oxo-, methyl ester



, which exhibit a phosphodiesterase inhibiting activity. Therefore, the instant claim is anticipated by Kouno et al.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Souness et al., Biochemical pharmacology, 1999, Vol. 58, pages 991-999. Souness et al. disclosed the instant claimed compound, which from the STN search is

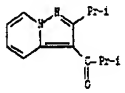
RN 50847-11-5
CN 1-Propanone, 2-methyl-1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-



, which exhibit a phosphodiesterase inhibiting activity. Therefore, the instant claim is anticipated by Souness et al.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Suzumura et al., Brain Research, 1999, Vol. 837, pages 203-212. Suzumura et al. disclosed the instant claimed compound, which from the STN search is

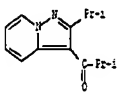
RN 50847-11-5
CN 1-Propanone, 2-methyl-1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-



, which exhibit a phosphodiesterase inhibiting activity. Therefore, the instant claim is anticipated by Suzumura et al.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kishi et al., Journal of cardiovascular pharmacology, 2000, Vol. 36, pages 65-70. Kishi et al. disclosed the instant claimed compound, which from the STN search is

RN 50847-11-5
CN 1-Propanone, 2-methyl-1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-



, which exhibit a phosphodiesterase inhibiting activity. Therefore, the instant claim is anticipated by Kishi et al.

10. ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

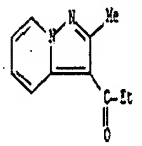
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 2 is rejected under 103(a) as being unpatentable over Kouno et al. of US 6,265,577.

Determination of the scope and content of the prior art (MPEP §2141.01)

Kouno et al. disclosed analogous compounds, which has the structure



Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claim and the prior art compound is that in the prior art compound R^1 being methyl and R^2 being ethyl substituents instead of the R^1 being isopropyl and R^2 being isopropyl in the instant application.

Finding of prima facia obviousness-rational and motivation (MPEP §2142.2143)

One having ordinary skill in the art would be motivated to modify the prior art compound to the instant compound. Because compounds that differ only by the presence or absence of an extra methylene group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologues. The homologue is expected to be prepared by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of

unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methylene groups. See *In re Wood,* 199 USPQ 137; *In re Hoke*, 195 USPQ 148, *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Wiechert*, 152 USPQ 249; *Ex parte Henkel*, 130 USPQ 474; *In re Fauque*, 121 USPQ; *In re Druey*, 138 USPQ 39.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI
07/24/2007
NR

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